(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2003 (26.06.2003)

PCT

(10) International Publication Number
WO 03/051871 A1

(51) International Patent Classification[7]: C07D 417/06, 211/34, 417/14, A61K 31/4545, A61P 3/04

(21) International Application Number: PCT/GB02/05675

(22) International Filing Date:
13 December 2002 (13.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0130388.2 19 December 2001 (19.12.2001) GB

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM PLC** [GB/GB]; 980 Great West Road, CN925.1, Brentford, Middlesex TW8 9GS (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRANCH, Clive, Leslie** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **JOHNS, Amanda** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **JOHNSON, Christopher, Norbert** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **NOVELLI, Riccardo** [IT/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **PORTER, Roderick, Alan** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **STEAD, Rachel, Elizabeth, Anne** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **STEMP, Geoffrey** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **THEWLIS, Kevin** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **HOCKLEY, Sian, Catherine**; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/051871 A1

(54) Title: N-AROYL CYCLIC AMINE DERIVATIVES AND THEIR USE AS ORXIN RECEPTOR ANTAGONIST

(57) Abstract: This invention relates to N-aroyl cyclic amine derivatives and their use as pharmaceuticals.

N-AROYL CYCLIC AMINE DERIVATIVES AND THEIR USE AS OREXIN RECEPTOR ANTAGONIST

This invention relates to *N*-aroyl cyclic derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as subarachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-

chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; nausea, vomiting; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

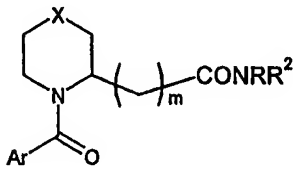
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides N-aroyl cyclic amine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders, and/or stroke, particularly ischemic or haemorrhagic stroke, and/or for blocking the emetic response i.e. useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577, and WO00/47580, disclose phenyl urea derivatives and WO00/47576, discloses quinolinyl cinnamide derivatives as orexin receptor antagonists.

According to the invention there is provided compounds of formula (I):



(I)

wherein:

X represents $(CH_2)n$, O or NR^1, wherein n represents 0, 1 or 2;

R^1 represents hydrogen or an optionally substituted (C_{1-6})alkyl;

m represents 1 or 2;

R represents an optionally substituted aryl, an optionally substituted 5- or 6- membered heteroaryl group containing up to 3 heteroatoms selected from N, O, and S, or an optionally substituted bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

R^2 represents hydrogen, or with R and the nitrogen to which they are attached form a 5- or 6- membered heterocyclic containing up to 3 heteroatoms selected from N, O, and S or an optionally substituted bicyclic heterocyclic or heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

Ar represents a phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heteroaryl group is substituted by R^3, and further optional substituents; or Ar represents an optionally substituted bicyclic aromatic or heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^3 independently represents hydrogen, an optionally substituted (C_{1-4})alkoxy, halo, an optionally substituted (C_{1-6})alkyl, an optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 3 heteroatoms selected from N, O and S;

or pharmaceutically acceptable derivatives thereof.

Examples of 5- or 6- membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, or pyrazolyl.

When R represents a bicyclic heteroaryl it may be selected from isoquinolinyl, quinoxalinyl, benzoxazolyl, quinolinyl, napththyridinyl, benzofuranyl, benzimidazolyl, quinazolinyl, indolyl, benzothienyl, benzothiazolyl or isoindolyl.

When R and R^2 together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring it can be pyrrolyl, imidazolyl, triazolyl, pyrazolyl, piperidine, piperazine, pyrrolidine, morpholine or thiomorpholine.

When R and R^2 together with the nitrogen to which they are attached form an optionally substituted bicyclic heterocyclic or heteroaryl it can be an indolyl, isoindolyl, benzimidazolyl, azaindolyl, azaisoindolyl or indazolyl.

Examples of where Ar represents an optionally substituted bicyclic aromatic or heteroaromatic include naphthyl, quinolinyl, napththyridinyl, benzofuranyl, benzimidazolyl, quinoxalinyl, quinazolinyl, isoquinolinyl or benzoxazolyl.

Preferably R^1 is hydrogen or methyl.

Preferably R represents phenyl.

Preferably X is CH_2

Preferably when Ar represents phenyl, or a 5-or 6- membered heteroaryl group the substituent R^3 is *ortho* to the amide carbonyl group.

Preferably Ar represents optionally substituted thiazolyl or phenyl.

Preferably R^2 is H or together with R and the nitrogen to which it is attached forms an indolyl or an isoindolyl.

Examples of groups where R^3 is a 5- or 6-membered heterocyclic ring containing up to 3 heteroatoms selected from N, O and S, include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, piperidine, morpholine, thiomorpholine or piperazine.

Preferably R^3 represents trifluoromethoxy, methoxy, ethoxy, halo, or optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl, or oxadiazolyl group.

Even more preferably R^3 represents an optionally substituted phenyl, e.g. 4-fluorophenyl.

When used herein the term amide carbonyl group means the -C(O)-N- bond as shown in compounds of formula (I).

Optional substituents for the groups R, R^2, $R^3$and Ar include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4})alkyl, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, (C_{1-4})acyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylamino(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkoxy, (C_{1-4})alkanoyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylsulfonyloxy, (C_{1-4})alkylsulfonyl(C_{1-4})alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl(C_{1-4})alkyl, (C_{1-4})alkylsulfonamido, (C_{1-4})alkylamido, (C_{1-4})alkylsulfonamido(C_{1-4})alkyl, (C_{1-4})alkylamido(C_{1-4})alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C_{1-4})alkyl, arylcarboxamido(C_{1-4})alkyl, aroyl, aroyl(C_{1-4})alkyl, or aryl(C_{1-4})alkanoyl group; a group R^aR^bN-, $R^aR^bN(CH_2)n$-, $R^aR^bN(CH_2)nO$-, $R^aOCO(CH_2)_r$, $R^aCON(R^b)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ or $R^aSO_2NR^b(CH_2)_r$ where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4})alkyl group or where appropriate R^aR^b forms part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring, n represents an interger from 1 to 4, and r represents zero or an integer from 1 to 4. Additionally when the substituent is $R^aR^bN(CH_2)n$- or $R^aR^bN(CH_2)nO$, R^a with at least one CH_2 of the $(CH_2)n$ portion of the group form a $(C_{3-}$

$_{6}$)azacycloalkane and R^b represents hydrogen, a (C_{1-4})alkyl group or with the nitrogen to which it is attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane.

Preferred optional substituents for Ar are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, $R^aR^bN(CH_2)n$ or R^aR^bN.

Preferred optional substituents for R or when R and R2 together with the nitrogen to which they are attached from a ring are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})acyl, (C_{1-4})alkoxy(C_{1-4})alkyl, $R^aR^bNCO(CH_2)_n$, $R^aR^bN(CH_2)n$, $R^aR^bN(CH_2)nO$ or R^aR^bN.

Preferred optional substituents for R^3 are halogen, (C_{1-4})alkoxy(C_{1-4})alkyl, R^aR^bN, $R^aR^bN(CH_2)n$ or $R^aR^bN(CH_2)nO$.

In addition R may be optionally substituted by a phenyl ring optionally substituted by a halogen, cyano, or C_{1-4}alkanoyl or C_{1-4}alkylsulfonyl group; or by a 5- or 6-membered heterocyclic ring, optionally substituted by a (C_{1-2})alkyl or R^aR^bN- group; wherein R^a and R^b are as defined above.

In the groups Ar and R, substituents positioned *ortho* to one another may be linked to form a fused ring.

When a halogen atom is present in the compound of formula (I) it may be fluorine, chlorine, bromine or iodine.

When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

When used herein the term aryl means a 5- to 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

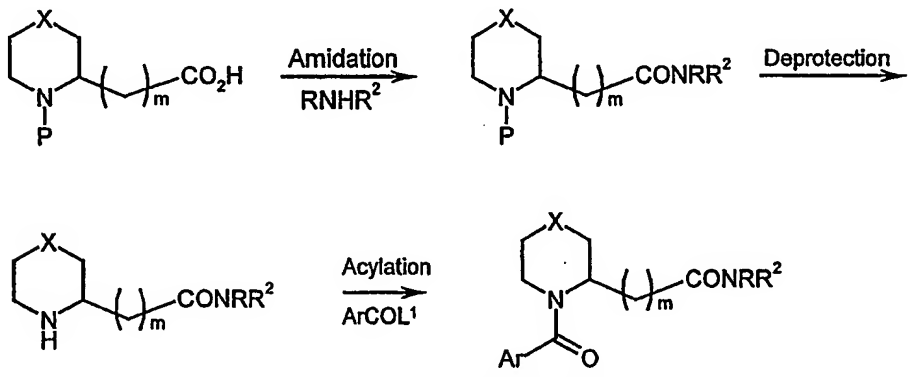
It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and salts thereof. The following schemes detail synthetic routes to compounds of the invention.

Scheme 1



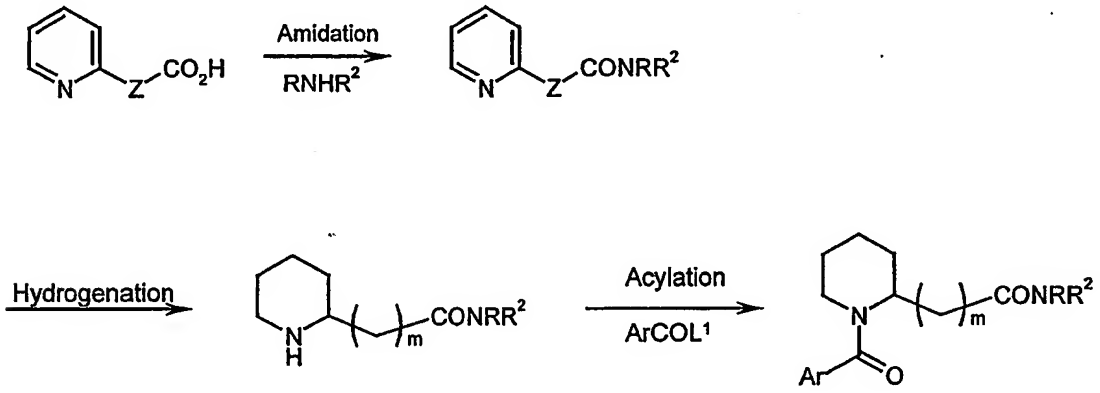
wherein X, Ar, R, R^2 and m are as defined for formula (I), P is a protecting group and L^1 is a leaving group.

Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl, benzyloxycarbonyl and optionally substituted benzyl. Deprotection conditions will depend on the particular protecting group; for the groups mentioned above these are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. potassium carbonate in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g. using palladium on charcoal in a lower alcohol or ethyl acetate).

Examples of suitable leaving groups L^1 include halogen, OC(=O)alkyl, OC(=O)O-alkyl and OSO_2Me. Acylation may be carried out using a wide range of known conditions, e.g. in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively these steps may be carried out when L^1 represents hydroxy, in which case the reaction takes place in an inert solvent such as dichloromethane or dimethylformamide in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole or *O*-(7-azabenzotriazol-1-yl)-N,N,N^1,N^1-tetramethyluronium hexafluorophosphate in the presence of a base such as N,N-diisopropylethylamine.

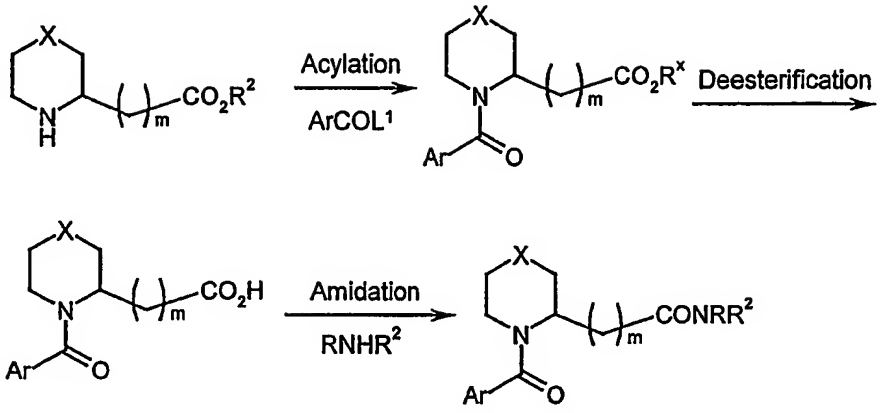
The amidation step can be accomplished using a wide range of known conditions, ie. conversion of the acid moiety into a suitable leaving group L^1 and subsequent reaction with the amine as described for the acylation step above.

Scheme 2



wherein Ar, R and R^2 are as defined for formula (I), L^1 is a leaving group as described for Scheme 1 and Z is $(CH_2)_m$ or -CH=CH- wherein m is as defined for formula (I)

Scheme 3



wherein X, Ar, R, R^2, and m are as defined for formula (I), L^1 is a leaving group as described for Scheme 1 and R^x is an optionally substituted (C_{1-6}) alkyl group. Within the scheme there is scope for functional group interconversion and interchange of protecting group.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity and diabetes; prolactinoma; hypoprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; bulimia and hypopituitarism. The compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in the treatment of stroke, particularly ischaemic or haemorrhagic stroke. Furthermore the compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in blocking the emetic response.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, sleep disorders, stroke and blocking the emetic response for example nausea and vomiting.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochloro-hydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Human orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu

1 5 10 15

Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr

20 25 30

Leu-NH_2

Orexin-A can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D8 illustrate the preparation of intermediates to compounds of the invention.

Abbreviation used herein are as follow:

HATU means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

DMF means *N,N*-dimethylformamide

MDC means dichloromethane

Description 1: (RS)-1-(*t*-Butyloxycarbonyl)-2-(phenylcarbamoylmethyl)piperidine

To (RS)-2-(1-*t*-butyloxycarbonylpiperidin-2-yl)acetic acid (1.99g, 8.2 mmol) in MDC (100ml) was added aniline (0.76g, 8.2 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (1.58g, 8.2 mmol) and 1-hydroxybenzotriazole (0.19g). After stirring at ambient temperature for 4h., the reaction mixture was washed sequentially with saturated aqueous sodium hydrogen carbonate, 1M hydrochloric acid and brine, dried (Na_2SO_4) and evaporated to give the title product as a pale yellow oil (1.68g, 94%). Mass spectrum (API$^+$): Found 219 (MH^+-^{t}Boc). $C_{18}H_{26}N_2O_3$ requires 318.

Description 2: (RS)-2-(Phenylcarbamoylmethyl)piperidine

A solution of D1 (2.4g, 7.7 mmol) in MDC (30 ml) and trifluoroacetic acid (6 ml) was stirred at 40°C for 2 h. The solution was evaporated and the resulting oil partitioned between 50% ether in hexane (100 ml) and 1M hydrochloric acid (100 ml). The aqueous layer was separated, basified with 5M sodium hydroxide and extracted with MDC (x3). The combined extracts were dried (Na_2SO_4) and evaporated to give the title product as an oil (1.25g, 76%). Mass spectrum (API$^+$): Found 219 (MH^+). $C_{13}H_{18}N_2O$ requires 218.

Description 3: (RS)-1-(*t*-Butyloxycarbonyl)-2-(((5-methoxycarbonyl)indol-1-yl)carbonylmethyl)piperidine

To (RS)-2-(1-*t*-butyloxycarbonylpiperidin-2-yl) acetic acid (2.29g, 10 mmol) in DMF (10 ml) was added methyl indole-5-carboxylate (0.98g, 5.6 mmol), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.92g, 10 mmol), 1-hydroxybenzotriazole (0.2g) and N,N-diisopropylethylamine (1.48g, 11.4 mmol). After stirring at ambient temperature for 18h, the reaction mixture was evaporated and the residual oil chromatographed on silica gel to afford the title compound (2.2g, 98%). Mass spectrum (API$^+$): Found 301 (MH^+-^{t}Boc). $C_{22}H_{28}N_2O_5$ requires 400.

Description 4: (RS)-2-(((5-Methoxycarbonyl)indol-1-yl)carbonylmethyl)piperidine

A solution of D3 (1.9g, 4.8 mmol) in MDC (20 ml) and trifluoroacetic acid (2 ml) was stirred at 50°C for 1h. The solution was evaporated and the resulting oil chromatographed on silica gel eluting with a 10:1 mixture of MDC and methanol/0.88 ammonia (10:1) to afford the title product (1.5g, 100%).

Description 5: (E)-*N*-(4-Fluorophenyl)-3-pyridin-2-yl-acrylamide

To 3-(pyridin-2-yl)prop-1-enoic acid (E. Alcalde *et al*, *Synthesis*, 1992, 395) (1g, 6.7 mmol) in MDC (20 ml) at ambient temperature was added 4-fluoroaniline (0.74g, 6.7 mmol), followed by 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (1.41g, 7.3 mmol), and 1-hydroxybenzotriazole (0.1g). After stirring for 18h, the reaction mixture was diluted with MDC (40

ml) and washed with saturated aqueous sodium hydrogen carbonate. The resulting suspension was filtered and the solid washed well with water, then ether and dried *in vacuo* to afford the title product as a white solid (1g, 61%). Mass spectrum (API^+): Found 243 (MH^+). $C_{14}H_{11}FN_2O$ requires 242. ^1H NMR ($CDCl_3$) δ: 6.99 - 7.07 (2H, m), 7.15 (1H, d, J = 15 Hz), 7.20 - 7.30 (1H, m), 7.35 - 7.40 (1H, m), 7.50 - 7.70 (3H, m), 7.70 - 7.76 (2H, m), 8.60 (1H, m).

Description 6: (RS)-*N*-(4-Fluorophenyl)-3-piperidin-2-yl-propionamide-hydrochloride

To D5 (1g, 4.1 mmol) in methanol (220 ml) was added 1M hydrogen chloride in ether (4.5 ml; 4.5 mmol) followed by platinum oxide catalyst (0.15 g). The mixture was hydrogenated at atmospheric pressure and ambient temperature for 3h. Filtration through kieselguhr and evaporation *in vacuo* afforded the title compound as a solid (1.2 g; 100%). Mass spectrum (API^+): Found 251 (MH^+). $C_{14}H_{19}FN_2O$ requires 250.

Description 7: (RS)-Methyl 2-(1-((4-(2-methyl-5-(4-fluorophenyl))thiazolyl)carbonyl) piperidin-2-yl)-acetate

A stirring solution of 2-methyl-5-(4-fluorophenyl)thiazole-4-carboxylic acid (3.0g, 12.5mmol) in DMF (50ml) under argon was treated sequentially with N,N-diisopropylethylamine (6.8ml, 39mmol), and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (4.77g, 12.5mmol). After stirring for 0.25h, methyl 2-(piperidin-2-yl)-acetate (Beckett et al, J.Med.Chem., 1969, 563,) (1.83g, 12.5mmol) was added. The mixture was stirred for 16h. at ambient temperature and was then diluted with water. The product was extracted into diethyl ether. The organic phase was washed with water (X3) and brine, dried ($MgSO_4$) and evaporated to afford the title compound as a yellow gum (4.0g, 85%). Mass spectrum (API^+) : Found 377 (MH^+). $C_{19}H_{21}FN_2O_3S$ requires 376.

Description 8: (RS) 2-(1-((4-(2-methyl-5-(4-fluorophenyl))thiazolyl)carbonyl) piperidin-2-yl)-acetic acid

To a stirring solution of D7 (4.0g, 10.6mmol) in methanol (75ml) and water (25ml) was added sodium hydroxide (0.85g, 21.3mmol). The mixture was stirred for 16h. at ambient temperature. The methanol was evaporated and the residue was diluted with water and extracted with diethyl ether (X2). The aqueous phase was acidified with 5N hydrochloric acid and the product was extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated. The residue was triturated with pentane to afford the title compound as a white solid (3.10g, 82%). ^1H NMR (D_6-DMSO) δ: 0.98 (0.6H, m), 1.15-1.70 (5.4H, bm), 2.18 (0.4H, dd), 2.38 (0.6H, dd, J = 6 and 15Hz), 2.70 (4.4H, m), 2.93 (0.6H, m), 3.17 (0.6H, d, J = 12Hz), 3.94 (0.4H, m), 4.40 (0.4H, d, J = 12Hz), 5.05 (0.6H, m), 7.27 (2H, m), 7.47 (2H, m), 12.20 (1H, bs).

Example 1: (RS)-1-((4-(2-Methyl-5-phenyl)thiazolyl)carbonyl)-2-(phenylcarbamoylmethyl)piperidine

A mixture of D2 (0.011g, 0.05 mmol), 2-methyl-5-phenylthiazole-4-carbonyl chloride (0.012g, 0.05 mmol), and triethylamine (0.005g, 0.05 mmol) in MDC (3 ml) was shaken for 0.75 h. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate, and the organic phase applied to a pre-packed silica gel cartridge and eluted with 30-100% ethyl acetate in hexane to

afford the title compound as a gum (0.012g, 59%). Mass spectrum (API^+):Found 420 (MH^+). $C_{24}H_{25}N_3O_2S$ requires 419.

Example 2: (RS)-1-((2-Phenyl)benzoyl)-2-(phenylcarbamoylmethyl)piperidine

The title compound was prepared, using the method of E 1, from D2 (0.011g, 0.05 mmol), 2-phenylbenzoyl chloride (0.011g, 0.05 mmol) and triethylamine (0.005g, 0.06 mmol) as a gum (0.018g, 90%). Mass spectrum (API^+): Found 399 (MH^+). $C_{26}H_{26}N_2O_2$ requires 398.

Example 3: (RS)-2-(((5-Methoxycarbonyl)indol-1-yl)carbonylmethyl)-1-((4-(2-methyl-5-(4-fluorophenyl))thiazolyl)carbonyl)piperidine

A mixture of D4 (0.3g, 1 mmol), 2-methyl-5-(4-fluorophenyl)thiazole-4-carboxylic acid (0.24g, 1 mmol), HATU (0.381g, 1 mmol), and N,N-diisopropylethylamine (0.23g, 1.7 mmol) in DMF (2ml) was stirred at ambient temperature for 18h. The reaction was evaporated and the residue partitioned between MDC and aqueous potassium carbonate solution. The organic extract was chromatographed on silica gel to afford the title compound (0.22g, 42%). Mass spectrum (API^+): Found 520 (MH^+). $C_{28}H_{26}FN_3O_4S$ requires 519.

Example 4: (RS)-2-(2-((4-Fluorophenyl)carbamoyl)ethyl)-1-((4-(2-methyl-5-phenyl)thiazolyl)carbonyl)piperidine

The title compound was prepared, using the method of E1, from D6 (0.05g, 0.17 mmol) and 2-methyl-5-phenylthiazole-4-carbonyl chloride (0.04g, 0.19 mmol), as a gum (0.046g, 59 %). Mass spectrum (Electrospray LC/MS): Found 452 (MH^+). $C_{25}H_{26}FN_3O_2S$ requires 451.

Example 5: (RS)-1-((2-Phenyl)benzoyl)-2-(2-((4-fluorophenyl)carbamoyl)-ethyl)piperidine

In a similar manner to E 4, the title compound was prepared as a gum (0.056g, 75%). Mass spectrum (Electrospray LC/MS): Found 431 (MH^+). $C_{27}H_{27}FN_2O_2$ requires 430.

Example 6: (RS)-2-((1,3-Dihydro-isoindol-2-yl)carbonylmethyl)-1-((4-(2-methyl-5-(4-fluorophenyl))thiazolyl)carbonyl)piperidine

The title compound was prepared, in a similar manner to that described in E 3, from D8 (0.167g, 0.46 mmol) and 1,3-dihydroisoindole hydrochloride (0.072g, 0.46 mmol), as a pale yellow solid (0.138g, 65%). Mass spectrum (API^+): Found 464 (MH^+). $C_{26}H_{26}FN_3O_2S$ requires 463.

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 90 min at 37°C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$$K_b = IC_{50}/(1+([3/EC_{50}])$$

where EC_{50} was the potency of human orexin-A determined in the assay (in nM terms) and IC_{50} is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values >7.0 at the human cloned orexin-1 receptor.

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$$Kb = IC50/(1+([3/EC50])$$

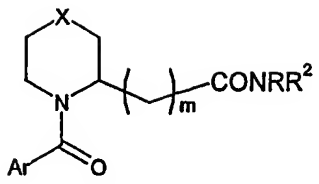
where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range 5.9 to 7.2 at the human cloned orexin-2 receptor.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

wherein:

X represents $(CH_2)n$, O or NR^1, wherein n represents 0, 1 or 2;

R^1 represents hydrogen or an optionally substituted (C_{1-6})alkyl;

m represents 1 or 2;

R represents an optionally substituted aryl, an optionally substituted 5- or 6- membered heteroaryl group containing up to 3 heteroatoms selected from N, O, and S, or an optionally substituted bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

R^2 represents hydrogen, or with R and the nitrogen to which they are attached form a 5- or 6- membered heterocyclic containing up to 3 heteroatoms selected from N, O, and S or an optionally substituted bicyclic heterocyclic or heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

Ar represents a phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heteroaryl group is substituted by R^3, and further optional substituents; or Ar represents an optionally substituted bicyclic aromatic or heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^3 independently represents hydrogen, an optionally substituted (C_{1-4})alkoxy, halo, an optionally substituted (C_{1-6})alkyl, an optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 3 heteroatoms selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R represents phenyl or R and R^2 together with the nitrogen to which they are attached form an indolyl or isoindolyl.

3. A compound according to claim 1 or 2 wherein Ar represents an optionally substituted thiazolyl or phenyl.

4. A compound according to any one of claims 1 to 3 wherein R^3 represents an optionally substituted phenyl.

5. The compound of any one of Examples 1 to 6 or a pharmaceutically acceptable salt of any one thereof.

6. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 02/05675

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/06 C07D211/34 C07D417/14 A61K31/4545 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 47576 A (JOHNS AMANDA ;PORTER RODERICK ALAN (GB); SMITHKLINE BEECHAM PLC (G) 17 August 2000 (2000-08-17) abstract	1,7
A	WO 01 68609 A (FISCHLI WALTER ;ACTELION PHARMACEUTICALS LTD (CH); CAPPI MICHAEL () 20 September 2001 (2001-09-20) abstract	1,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2003	27/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	de Nooy, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 02/05675

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ıational Application No
PCT/GB 02/05675

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0047576 A	17-08-2000	WO 0047576 A1	17-08-2000
WO 0168609 A	20-09-2001	AU 6011301 A	24-09-2001
		WO 0168609 A1	20-09-2001
		EP 1274687 A1	15-01-2003
		NO 20024339 A	11-09-2002